U.S. FOOD & DRUG ADMINISTRATION

Memorandum

DATE: January 06, 2023

TO: Niloofar Kennedy, RPM, CBER/OTAT/DRPM/RPMB3
Zuben Sauna, Ph.D., Committee Chair, CBER/OTAT/DPPT/HB
Megha Kaushal, M.D., Clinical Reviewer, CBER/OTAT/DCEPT/BHB

FROM: Kristine Khuc, Pharm.D.
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Advertising and Promotional Labeling Branch (APLB)
Division of Case Management (DCM)
Office of Compliance and Biologics Quality (OCBQ)

THROUGH: Lisa L. Stockbridge, Ph.D.
Branch Chief
APLB/DCM/OCBQ

SUBJECT: **ALTUVIIIO [antihemophilic factor (recombinant), Fc-Von Willebrand factor, XTEN fusion protein]**
BLA: 125771/0
Sponsor: Bioverativ Therapeutics, Inc.

Background

The sponsor submitted:
_x_ New Approval
___ Changes Being Effected (CBE) supplement
___ Prior Approval Supplement (PAS)
___ Major Amendment

Submission contains:
_x_ Prescribing Information (PI)
_x_ Patient Package Insert (PPI)
_x_ Package and/or container labels
___ Other

Submission Date: May 12, 2022

PDUFA Action Date: **February 28, 2023**

APLB Comments/Recommendations

This labeling review is for an original Biologics License Application submitted by Bioverativ Therapeutics, Inc. for ALTUVIIIO [antihemophilic factor (recombinant), Fc-Von Willebrand factor, XTEN fusion protein]. APLB reviewed the draft labeling, submitted by Bioverativ Therapeutics on June 30, 2022, from a comprehension and promotional perspective.

GENERAL

- Use lower case letters for the proper name of this product. In addition, add the suffix to the proper name.

- There are different fonts for the sub-subsection headers and body text throughout the entire PI. Please use the same font for all text to enhance readability.

HIGHLIGHTS (HL)

- In the PRODUCT TITLE, revise the route of administration to “for intravenous use.” In other parts of the labeling, the route of administration can be more specific.

- In the INDICATIONS AND USAGE section, avoid promotional qualifiers characterizing the product as “long-acting” and “with high sustained FVIIII activity.”

- Revise the administration directive to be specific and consistent with the directive in subsection 2.3 Administration. For example,

  For intravenous injection after reconstitution only.

- Delete the Revision Date because this will be the original approval.

FULL PRESCRIBING INFORMATION: CONTENTS

Ensure that the table of contents is consistent with any changes to the FULL PRESCRIBING INFORMATION.

FULL PRESCRIBING INFORMATION (FPI)

INDICATIONS AND USAGE

Please refer to the comment in the HIGHLIGHTS section about avoiding the use of promotional qualifiers.

DOSAGE AND ADMINISTRATION

- Directly underneath the header, revise the administration directive to be consistent with the directive under the Administration subsection.

- Revise this section using active voice and command language whenever possible.

- Write out numerals under ten.

- Revise the Preparation and Reconstitution subsection using language directed towards healthcare professionals. For example, it is unnecessary to define the terms “aseptic,” “reconstitute,” and “dispose of.”

- Within subsection 2.2, consider adding figures to steps 8 through 14 to enhance comprehension.

- In subsection 2.3, be consistent and use the same administration directive as the one appearing in the HIGHLIGHTS section.

- Consider adding figures to the Administration steps in subsection 2.3.

DOSAGE FORMS AND STRENGTHS

For clarity, add the color of the solution once reconstituted.

CONTRAINDICATIONS

For clarity, revise the term “components” to “excipients.” Add a cross-reference to section 11 stating the excipients of the product.

WARNINGS AND PRECAUTIONS

Under subsection 5.2, the first sentence minimizes the risk that neutralizing antibodies (inhibitors) may occur with this particular product. Please revise this sentence to specifically state the inhibitors may occur with the use of ALTUVIIIO.

ADVERSE REACTIONS

- Delete information pertaining to an “adverse event.” Only include information regarding adverse reactions, which by definition is an adverse event where there is some basis to believe the event is related to the product.

- Underneath subsection 6.1, maintain product class labeling and add immunogenicity information under the Immunogenicity subheader. Within this subsection, cross-reference to subsection 12.6 for additional information.

CLINICAL PHARMACOLOGY

- Underneath subsection 12.1, the first sentence seems a little wordy. Simplify it by deleting the redundant phrase describing the “recombinant fusion protein.”

- Underneath the Mechanism of Half-Life Extension sub-subsection, it states that the protein is “designed to be independent of endogenous VWF in order to overcome the half-life limit imposed by FVIII-VWF interactions.” The term “designed” sounds promotional in tone. We recommend deleting it.

- Spell out the abbreviation “PK” the first time it is used.

- Within subsection 12.2 Pharmacodynamics, in the last statement, there is an efficacy superiority claim regarding ALTUVIIIO compared to existing FVIII products. Is this claim adequately supported by data? Otherwise, please delete.

- In subsection 12.3 Pharmacokinetics (PK), avoid using research terminology such as “Phase 1/2a” or “Phase 3.” Also, avoid using study names, which may decrease readability. Simply describe each study. Additionally, there is a comparative PK study of other factor VIII products. Comparisons of the PK of other products should not be in the instructions for the safe and effective of ALTUVIIIO.

- Subsection12.6 describes immunogenicity information. Preceding the presentation of the data, add the regulatory language regarding differences in assays. Describe additional immunogenicity data (e.g., duration of exposure, assay sampling time) on the clinically insignificant effect reported.

CLINICAL STUDIES

- Avoid using study names, such as “XTEND-1” or “XTEND-Kids,” which may decrease readability. Instead, just describe each study.

- There are lengthy descriptions of (b) (4) If not, please revise or delete these descriptions in the CLINICAL STUDIES section.

PACKAGE AND CONTAINER LABELS

Add the suffix to the proper name of the product.

PATIENT PACKAGE INSERT

PATIENT INFORMATION

- For consistency with the PI, revise the indication to state that ALTUVIIIO is an injectable medicine that is used to control and “reduce the number of bleeding episodes,” instead of “prevent bleeding.”

- Underneath the header titled “What are the possible side effects of ALTUVIIIO,” use consumer-friendly language. For example, revise the term “arthralgia” to “joint pain.”

- Revise the color code scheme of the product to be consistent with the color scheme described in the PI. For example, revise the color “Blue” to “Royal Blue.”

INSTRUCTIONS FOR USE

- Revise the IFU to the following recommended headers described in the *Guidance for Industry: Instructions for Use- Patient Labeling for Human Prescription Drug and Biological Products- Content and Format.* Please refer to the guidance for additional recommendations when revising this document. For example,

  Visual of Drug Product
  Important Information for Patients
  Preparation Instructions
  Administration Instructions
  Storage Instructions
  Disposal Instructions

- On the last line of this document, include the date of initial approval (i.e., February 2023).

If you have any questions regarding this review, please contact Kristine T. Khuc, Pharm.D., Consumer Safety Officer at (240) 402-8982.